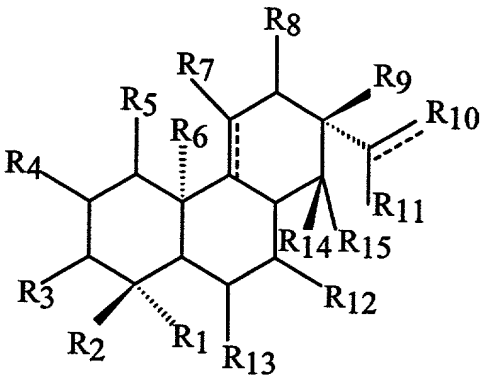
NOVEL INTERLEUKIN-1 AND TUMOR NECROSIS FACTOR-α MODULATORS, SYNTHESES OF SAID MODULATORS AND METHODS OF USING SAID MODULATORS

Abstract of the Disclosure

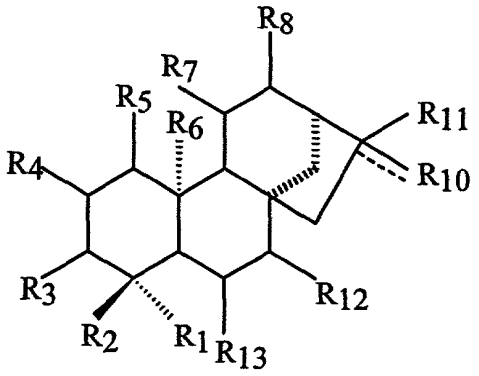
Novel compounds are disclosed that have the chemical structure of Formula (II), and its prodrug esters and acid-addition salts, and that are useful as Interleukin-1 and Tumor Necrosis Factor-α modulators, and thus are useful in the treatment of various diseases.



(II)

wherein the R groups are defined as follows: if any R_3-R_5, R_7, R_8, R_{11}-R_{13} is not hydrogen, R_2 or R_6 or R_9 is not methyl, or R_{10} is not CH_2, then R_1 is selected from the group consisting of hydrogen, a halogen, COOH, C_1-C_{12} carboxylic acids, C_1-C_{12} acyl halides, C_1-C_{12} acyl residues, C_1-C_{12} esters, C_1-C_{12} secondary amides, (C_1-C_{12})(C_1-C_{12}) tertiary amides, C_1-C_{12} alcohols, (C_1-C_{12})(C_1-C_{12}) ethers, C_1-C_{12} alkyls, C_1-C_{12} substituted alkyls, C_2-C_{12} alkenyls, C_2-C_{12} substituted alkenyls, and C_5-C_{12} aryls. If all R_3-R_5, R_7, R_8, R_{11}-R_{13} are hydrogen, R_2, R_6, and R_9 are each methyl, and R_{10} is CH_2, then R_1 is selected from hydrogen, a halogen, C_1-C_{12} carboxylic acids, C_1-C_{12} acyl halides, C_1-C_{12} acyl residues, C_2-C_{12} esters, C_2-C_{12} secondary amides, (C_1-C_{12})(C_1-C_{12}) tertiary amides, C_2-C_{12} alcohols, (C_1-C_{12})(C_1-C_{12}) ethers other than methyl-acetyl ether, C_2-C_{12} alkyls, C_1-C_{12} substituted alkyls, C_2-C_{12} alkenyls, C_2-C_{12} substituted alkenyls, and C_2-C_{12} aryls. R_2 and R_9 are each separately selected from hydrogen, a halogen, C_1-C_{12} alkyl, C_1-C_{12} substituted alkyls, C_2-C_{12} alkenyl, C_2-C_{12} substituted alkenyl, C_2 - C_{12} alkynyl, C_1-C_{12} acyl, C_1-C_{12} alcohol, and C_5-C_{12} aryl. R_3-R_5, R_7, R_8, and R_{11}-R_{13}

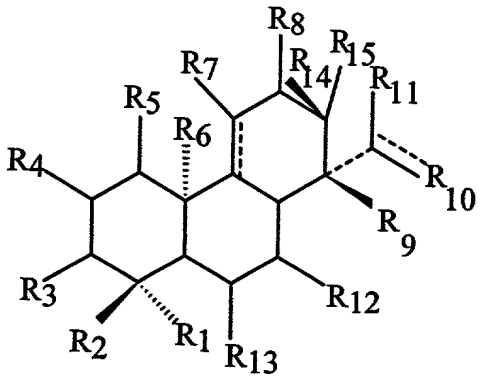
are each separately selected from hydrogen, a halogen, C_1-C_{12} alkyl, C_1-C_{12} substituted alkyls, C_2-C_{12} alkenyl, C_2-C_{12} substituted alkenyl, C_2-C_{12} alkynyl, and C_5-C_{12} aryl. R_6 is selected from hydrogen, a halogen, C_1-C_{12} alkyl, C_1-C_{12} substituted alkyls, C_2-C_{12} alkenyl, C_2-C_{12} substituted alkenyl, and C_2-C_{12} alkynyl. R_{10} is selected from hydrogen, a halogen, CH_2, C_1-C_6 alkyl, C_1-C_6 substituted alkyl, C_2-C_6 alkenyl, C_2-C_6 substituted alkenyl, C_1-C_{12} alcohol, and C_5-C_{12} aryl. Furthermore, novel compounds that have the chemical structure of Formula (IIA) and its prodrug esters and acid-addition salts are disclosed, and that are useful as Interleukin-1 and Tumor Necrosis Factor-α modulators, and thus are useful in the treatment of various diseases..



(IIA)

wherein the R groups are defined as follows: If any R_3-R_5, R_7, R_8, R_{11}-R_{13} is not hydrogen, R_2 or R_6 is not methyl, R_{10} is not CH_2, or if it is not true that R_{10} is CH_2OH and R_{11} is OH, then R_1 is selected from the group consisting of hydrogen, a halogen, COOH, C_1-C_{12} carboxylic acids, C_1-C_{12} acyl halides, C_1-C_{12} acyl residues, C_1-C_{12} esters, C_1-C_{12} secondary amides, (C_1-C_{12})(C_1-C_{12}) tertiary amides, C_1-C_{12} alcohols, (C_1-C_{12})(C_1-C_{12}) ethers, C_1-C_{12} alkyls, C_1-C_{12} substituted alkyls, C_2-C_{12} alkenyls, C_2-C_{12} substituted alkenyls. However, if all R_3-R_5, R_7, R_8, R_{11}-R_{13} are hydrogen, R_2 and R_6 are each methyl, and R_{10} is CH_2 or CH_2OH, then R_1 is selected from hydrogen, a halogen, C_1-C_{12} carboxylic acids, C_1-C_{12} acyl halides, C_1-C_{12} acyl residues, C_2-C_{12} esters, C_1-C_{12} secondary amides, (C_1-C_{12})(C_1-C_{12}) tertiary amides, C_2-C_{12} alcohols, (C_1-C_{12})(C_1-C_{12}) ethers, C_2-C_{12} alkyls, C_2-C_{12} substituted alkyls, C_2-C_{12} alkenyl, and C_2-C_{12} substituted alkenyl. R_2 is selected from hydrogen, a halogen, C_1-C_{12} alkyl, C_1-C_{12} substituted alkyls, C_2-C_{12} alkenyl, C_2-C_{12} substituted alkenyl, C_2 - C_{12} alkynyl, and C_1-C_{12} acyl, and C_5-C_{12} aryl. R_3, R_4, R_5, R_7, R_8, and R_{11}-R_{13} are each separately

selected from hydrogen, a halogen, C_1-C_{12} alkyl, C_1-C_{12} substituted alkyls, C_2-C_{12} alkenyl, C_2-C_{12} substituted alkenyl, C_2-C_{12} alkynyl, and C_5-C_{12} aryl. R_6 is selected from hydrogen, a halogen, C_1-C_{12} alkyl, C_1-C_{12} substituted alkyls, C_2-C_{12} alkenyl, C_2-C_{12} substituted alkenyl, and C_2-C_{12} alkynyl. R_{10} is selected from hydrogen, a halogen, CH_2, C_1-C_6 alkyl, C_1-C_6 substituted alkyl, C_2-C_6 alkenyl, C_2-C_6 substituted alkenyl, C_1-C_{12} alcohol, and C_5-C_{12} aryl. Pharmaceutical compositions comprising a therapeutically effective amount of acanthoic acid or of the compounds of Formula (II) and Formula (IIA), and a pharmaceutically acceptable carrier, are also disclosed, and are useful as anti-inflammatory analgesics, in treating immune disorders, as anti-cancer and anti-tumor agents, and in the treatment of cardiovascular disease, skin redness, diabetes, transplant rejection, otitis media, sinusitis, and viral infection. Furthermore, novel compounds that have the chemical structure of Formula (IIB) and its prodrug esters and acid-addition salts are disclosed, and are useful as Interleukin-1 and Tumor Necrosis Factor-α modulators, and thus are useful in the treatment of various diseases.



(IIB)

wherein the R groups include the following: R_1 is selected from the group consisting of hydrogen, a halogen, COOH, C_1-C_{12} carboxylic acids, C_1-C_{12} acyl halides, C_1-C_{12} acyl residues, C_1-C_{12} esters, C_1-C_{12} secondary amides, (C_1-C_{12})(C_1-C_{12}) tertiary amides, C_1-C_{12} alcohols, (C_1-C_{12})(C_1-C_{12}) ethers, C_1-C_{12} alkyls, C_1-C_{12} substituted alkyls, C_2-C_{12} alkenyls, C_2-C_{12} substituted alkenyls; R_2 is selected from hydrogen, a halogen, C_1-C_{12} alkyl, C_1-C_{12} substituted alkyls, C_2-C_{12} alkenyl, C_2-C_{12} substituted alkenyl, C_2 - C_{12} alkynyl, and C_1-C_{12} acyl, and C_5-C_{12} aryl. R_3, R_4, R_5, R_7, R_8, and R_{11}-R_{13} are each separately selected from hydrogen, a halogen, C_1-C_{12} alkyl, C_1-C_{12} substituted alkyls, C_2-C_{12} alkenyl, C_2-C_{12} substituted alkenyl, C_2-C_{12} alkynyl, and C_5-C_{12} aryl. R_6 is

selected from hydrogen, a halogen, C_1-C_{12} alkyl, C_1-C_{12} substituted alkyls, C_2-C_{12} alkenyl, C_2-C_{12} substituted alkenyl, and C_2-C_{12} alkynyl. R_{10} is selected from hydrogen, a halogen, CH_2, C_1-C_6 alkyl, C_1-C_6 substituted alkyl, C_2-C_6 alkenyl, C_2-C_6 substituted alkenyl, C_1-C_{12} alcohol, and C_5-C_{12} aryl. The disclosed compounds include the prodrug esters of the above compounds, and the acid-addition salts thereof. The disclosed compounds include the prodrug esters of the above compounds, and the acid-addition salts thereof. Pharmaceutical compositions comprising a therapeutically effective amount of the novel compounds of Formulae (II) and (IIA), and their prodrug esters, and a pharmaceutically acceptable carrier, are also disclosed, and are useful as anti-inflammatory analgesics, in treating immune disorders, as anti-cancer and anti-tumor agents, and in the treatment of cardiovascular disease, skin redness, and viral infection. Completely synthetic and semi-synthetic methods of making the compounds of Formulae (I) and (II), and their analogs, and the compounds of Formulae (II), (IIA) and (IIB) are disclosed, as are methods of using these synthetic and semi-synthetic compounds in the treatment of the above-listed disease states.

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